A New Efficient Method for the Preparation of Sulfone-Functionalized Prenylhydroquinones

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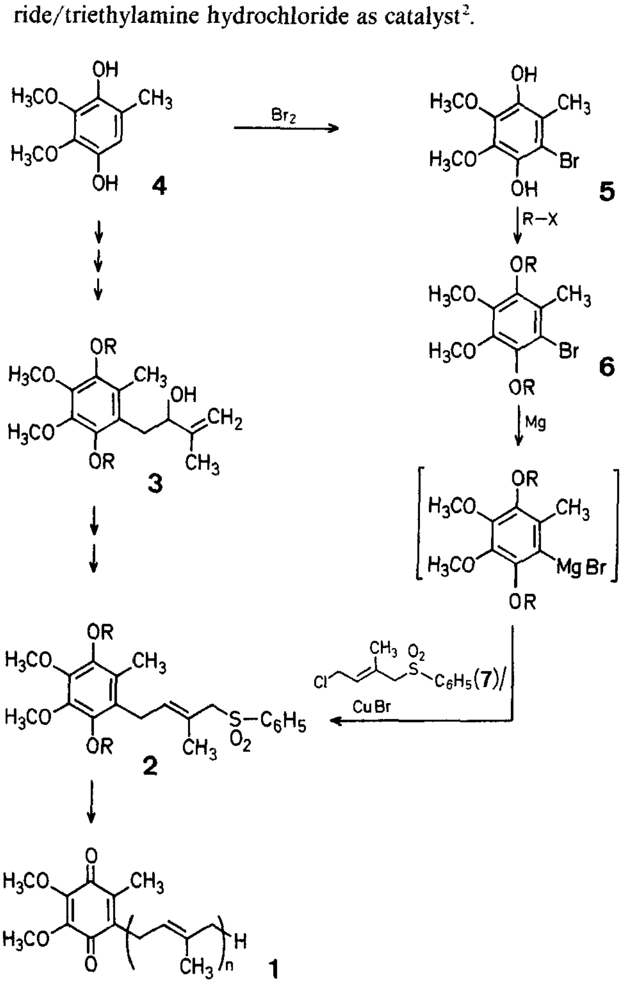
Recently, Terao et al. reported an advantageous and highly stereoselective synthesis of all-(*E*)-ubiquinone-10 (**1**; n = 10) using a sulfone-functionalized prenyl hydroquinone (**2**; R = C_6H_5—CH_2—) as a key-intermediate[1] and in which the allylic rearrangement **3**→**2** played an important role in controlling the stereoselective formation of (*E*)-**2**. However, the multi-step procedures required to synthesize **2** from hydroquinone **4** have considerably reduced the synthetic utility of this process, in particular for industrial use. We describe here a new efficient method for the preparation of **2** using (*E*)-4-chloro-2-methyl-1-phenylsulfonyl-2-butene (**7**) as a building block. This latter compound is conveniently obtained from the reaction of isoprene with benzenesulfonyl chloride in the presence of copper(I) chloride/triethylamine hydrochloride as catalyst[2].



The known two-step synthesis of 6-bromo-2,3-dimethoxy-5-methylhydroquinone[3] (**5**) requires troublesome handling and results in relatively low yield. We therefore recommend the following new simpler process which affords **5** in quantitative yield: addition of bromine to a solution of **4** in chloroform under a stream of nitrogen at room temperature. Hydroquinone **5** is then converted into the disodium derivative using sodium hydride; reaction of the disodium derivative with chloromethyl 2-methoxyethyl ether[4] in dry dimethylformamide (−20 °C, 2 h) affords **6c** (R = —CH_2—O—CH_2—CH_2—OCH_3) in ~90%

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Table. (3-Methyl-4-phenylsulfonyl)-hydroquinone Ethers

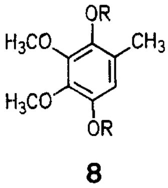
Substrate (R =) [mmol]	CuBr [mmol]	7 [mmol]	Method[a]	Yield [%][b]	Physical data	Molecular formula[c]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]
6a (CH$_3$)					m.p. 74–75°	$C_{22}H_{28}O_6S$ (420.5)	1.85 (s, 3H); 1.90 (s, 3H); 3.15 (d, 2H, J=7 Hz); 3.63, 3.70, 3.80, 3.83 (s, 12H); ~3.6–3.9 (—, 2H); 4.85 (t, 1H, J=7 Hz); 7.2–7.7 (m, 5H)
20	0	10	A	0			
20	2	10	A	13			
20	5	10	A	24			
20	10	10	A	48			
20	20	10	A	73			
6b (—CH$_2$—OCH$_3$)[5]					liquid	$C_{24}H_{32}O_8S$ (480.6)	1.87 (s, 3H); 1.97 (s, 3H); 3.23 (d, 2H, J=7 Hz); 3.45, 3.53, 3.76, 3.80 (s, 12H); 3.65 (s, 2H); 4.90, 4.97 (s, 4H); ~4.8–5.1 (m, 1H); 7.2–7.8 (m, 5H)
15	15	15	B	70			
30	30	15	A	64			
6c (MEM)					liquid	$C_{28}H_{40}O_{10}S$ (568.7)	1.87 (s, 3H); 1.97 (s, 3H); ~3.0–4.0 (m, 24H); 5.00, 5.07 (s, 4H); ~4.9–5.2 (m, 1H); ~7.2–7.8 (m, 5H)
500	500	500	B	82			
9a (CH$_3$)[6]					m.p. 156–157°	$C_{24}H_{26}O_4S$ (410.5)	1.93 (s, 3H); 2.13 (s, 3H); 3.40 (d, 2H, J=7 Hz); 3.65, 3.72, 3.78 (s, 8H); 4.96 (t, 1H, J=7 Hz); ~7.2–8.1 (m, 5H)
16	16	7	A	72			
16	16	16	B	82			
9b (—CH$_2$—OCH$_3$)					m.p. 73–75°	$C_{26}H_{30}O_6S$ (470.6)	1.90 (s, 3H); 2.16 (s, 3H); 3.53, 3.60 (s, 6H); ~3.4–3.6 (m, 4H); 4.91, 5.00 (s, 4H); ~4.9–5.1 (broad t, 1H); 7.18–8.0 (m, 9H)
20	20	20	B	70			
9c (MEM)					liquid	$C_{30}H_{38}O_8S$ (558.7)	1.83 (s, 3H); 2.10 (s, 3H); 3.25 (s, 6H); 3.32–3.9 (m, 16H), ~4.8–5.1 (m, 1H); ~5.9–8.1 (m, 9H)
20	20	20	B	82			
10a (CH$_3$)[7]					m.p. 127–129°	$C_{22}H_{28}O_4S$ (388.5)	1.90 (s, 3H); 1.96, 2.13 (s, 9H); 3.27 (d, 2H, J=7 Hz); 3.50, 3.58 (s, 6H); 3.66 (s, 2H); 4.93 (t, 1H, J=7 Hz); ~7.2–7.8 (m, 5H)
30	30	15	A	70			
30	30	30	B	79			
10b (—CH$_2$—OCH$_3$)					m.p. 98–99°	$C_{24}H_{32}O_6S$ (448.6)	1.87 (s, 3H); 1.96, 2.10, 2.12 (s, 9H); 3.27 (d, 2H, J=7 Hz); 3.46, 3.53, 3.63 (s, 8H); 4.77, 4.78 (s, 4H); 4.93 (t, 1H, J=7 Hz); ~7.2–7.8 (m, 5H)
15	15	15	B	71			

[a] Method A: Grignard reagent is added dropwise (slowly) to a mixture of **7** and copper(I) bromide.
B: A solution of **7** in tetrahydrofuran is added to the copper derivative prepared from of Grignard reagent and copper(I) bromide.

[b] Yield based on **7**.

[c] All products gave satisfactory microanalyses: C, ±0.30; H, ±0.25.

yield. Reaction of the Grignard derivative of **6** with **7** under various conditions afforded no trace of **2**; instead, the debrominated hydroquinone **8** was formed in nearly quantitative yield.



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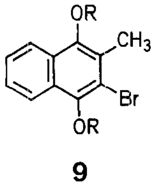

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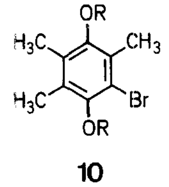

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The coupling reaction of the Grignard derivative of **6** with **7** could be achieved, however, in the presence of copper(I) bromide in amounts of 10, 25, and 50 mol% vs. **6** to give **2** in 13, 24, and 48% yields, respectively. The best yield was achieved when the Grignard derivative of **6** was converted into the corresponding arylcopper derivative. With the addition of copper(I) bromide, the reaction proceeds stereoselectively to give **2** exclusively in the (*E*)-form.

Among the various types of hydroquinone-protecting groups we have chosen the 2-methoxyethoxymethyl (MEM) group for industrial use (ubiquinone-10) because of the following facts: In the case of **6a**, the selective removal of the *O*-methyl groups appears to be difficult, and in the case of compound **6b** (which has been reported[5] to be unstable) elimination of the protective groups from the resultant **2b** proceeds to a certain extent during work-up of the reaction mixture. On the other hand, the *O*-2-methoxyethoxymethyl (MEM) group is relatively resistant to the usual acidic conditions (acetic acid, hydrochloric acid) but it can be selectively removed by heating with hydrobromic acid in ethanol.

The versatility of the present method was also confirmed by introduction of a sulfone-functionalized isoprene moiety into the aromatic systems of **9a, b, c** and **10a, b**.

6-Bromo-2,3-dimethoxy-5-methylhydroquinone (5):

The reaction should be carried out in a hood because of the formation of hydrogen bromide. To a stirred solution of 2,3-dimethoxy-5-methylhydroquinone (**4**; 184 g; 1 mol) in chloroform (600 ml), bromine (160 g, 1 mol) is added dropwise at room temperature during 1.5 h under a nitrogen stream. Stirring is continued for 1 h; then, the reaction mixture is washed with water (3 × 100 ml) and dried with magnesium sulfate. Removal of solvent under reduced pressure gives **5** as a gray solid mass; yield: 256.8 g (98%); m.p. 72–74 °C (Ref.[3], m.p. 73–74 °C).

6-Bromo-2,3-dimethoxy-5-methylhydroquinone Bis[2-methoxyethoxymethyl ether] (6c):

A 50% sodium hydride suspension (106 g, 2.2 mol) in mineral oil is added in small portions to a stirred solution of 6-bromo-2,3-dimethoxy-5-methylhydroquinone (**5**; 262.9 g, 1 mol) in dimethylformamide (4 l) at −20 °C. Then, chloromethyl 2-methoxyethyl ether (273 g, 2.2 mol) is added dropwise over a 2 h period, the mixture is allowed to warm to room temperature, and stirring is continued for 1 h. Ethanol (100 ml) is then added and the mixture poured into ice/water (1500 ml). The resultant mixture is extracted with ether (2 × 1500 ml) and the extract dried with magnesium sulfate. The ether is evaporated and the residual product purified by column chromatography on silica gel using dioxan/hexane (3/7) as eluent to give **6c** as a colorless oil; yield: 400 g (91%).

$C_{17}H_{27}BrO_8$	calc.	C 46.48	H 6.19
(439.3)	found	46.24	5.97

I.R. (neat): ν = 2930, 2875, 1458, 1410, 1385, 1080, 966 cm^{-1}.

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^{1}H-N.M.R. ($CDCl_3$/TMS, 100 MHz): $\delta = 2.26$ (s, 3H); 3.33 (s, 6H); 3.80 (s, 6H); 3.5–3.6, 3.8–4.1 (m, 8H); 5.07, 5.15 ppm (s, 4H).

6-(3-Methyl-4-phenylsulfonyl-2-butenyl)-1,2,3,4-tetramethoxy-5-methylbenzene (2a):

Method A: A solution of the Grignard reagent prepared from **6a** (8.78 g, 20 mmol) in dry tetrahydrofuran (100 ml) is added dropwise to a stirred mixture of copper(I) bromide (2.87 g, 20 mmol) and (*E*)-4-chloro-2-methyl-1-phenylsulfonyl-2-butene[2] (**7**; 2.44 g, 10 mmol) in tetrahydrofuran (100 ml) at 0 °C over a 2 h period. Stirring is continued for 2 h, the mixture poured into saturated ammonium chloride solution (50 ml) and extracted with ether (3 × 300 ml). The extract is dried with magnesium sulfate and evaporated. The residual product is purified by column chromatography on silica gel using chloroform as eluent to give **2a** as a colorless solid; yield: 3.07 g (73%, based on **7**); m.p. 74–75 °C.

$C_{22}H_{28}O_6S$	calc.	C 62.84	H 6.71
(420.5)	found	62.69	6.53

2,3-Dimethoxy-5-methyl-6-(3-methyl-4-phenylsulfonyl-2-butenyl)-hydroquinone Bis[2-methoxyethoxymethyl ether] (2c):

Method B: Powdered copper(I) bromide (71.7 g, 0.5 mol) is added to a stirred solution of the Grignard reagent prepared from **6c** (220 g, 0.5 mol) in tetrahydrofuran (2 l) at 10–15 °C and stirring is continued for 40 min. Then, a solution of (*E*)-4-chloro-2-methyl-1-phenylsulfonyl-2-butene[2] (**7**; 122 g, 0.5 mol) in tetrahydrofuran (300 ml) is added and stirring is continued at 20 °C for 2 h. The mixture is poured into saturated ammonium chloride solution (1300 ml) and extracted with ether (3 × 800 ml). The extract is dried with magnesium sulfate and evaporated. The residual product is purified by column chromatography on silica gel using chloroform as eluent to give **2c** as a viscous colorless oil; yield: 233 g (82%, based on **7**).

$C_{28}H_{40}O_{10}S$	calc.	C 59.14	H 7.09
(568.7)	found	58.97	6.88

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